REMARKS

Status of the Claims

Claims 1, 2, 4-8, 10-15, 17-19 and 22-32 are in the application.

Claims 1-2, 4-8, 10-15 and 17-19, 22-32 has been rejected.

Claim 1 has been objected to.

By way of this amendment, claims 1, 7, 15, and 22-24 have been amended. Claim 8 has been canceled.

Upon entry of this amendment, claims 1, 2, 4-7, 10-15, 17-19 and 22-32 will be pending.

Summary of the Amendment

Claim 1 and 22-24 have been amended to recite the invention more precisely and correct obvious typographical errors. Support for the amendment is found throughout the specification and claims as originally filed.

Claim 7 and 15 have been amended to more clearly recite the distinct sequences that encode an immunogen and OX40. Support for the amendment is found throughout the specification and claims as originally filed, but particularly the subject matter of claim 8.

No new matter has been added.

Claim Objection

Claim 1 stand objected to for failure to properly use correct grammatical symmetry. Claim 1 has been amended to correct the obvious typographical errors related to tense and grammar. As amended, the claims is more precisely written. Applicants respectfully request that the objection of claim 1 be withdrawn.

Claim Rejections under 35 USC § 102

Claims 7, 10-12, 14, 15, 17, 23-29, 31, and 32 stand rejected under 35 U.S.C. 102 (b) as being anticipated by US Patent No. 6,344,445 (Boursnell et al.). Applicants respectfully disagree with the Office assertion, but solely in the interest of expediting prosecution Applicants have

amended claim 7 to include the term "plasmid." Claims 10 – 12, 23, 25, 26, 28, and 31 depend on claim 7. Applicants have amended claim 15 to recite a composition comprising a recombinant vaccine and a separate nucleic acid sequence. Claims 24, 29, and 32 depend on claim 15. The amendments to claims 7 and 15 obviate the basis of the rejection as it applies to claim 7, 10-12, 23-26, 18, 19, 31, and 32. Applicants respectfully request that the rejection of claims 7, 10-12, 23-26, 18, 19, 31, and 32 is withdrawn.

Applicants respectfully request a clarification of the rejection of claims 14 and 27. Both claims are dependent upon claim 1 and claim 1 was not rejected. Applicants have assumed for purposes of this response that the Office has made an error.

Claims 7, 8, 10, 15, 17, 23, 24, 28, 29, 31, and 32 stand rejected stand rejected under 35 U.S.C. 102 (b) as being anticipated by US Patent No. 6,017,735 (O'Hare et al.). Applicants respectfully disagree with the Office assertion, but solely in the interest of expediting prosecution Applicants have amended claim 7 to include the term "plasmid." Claims 10 – 12, 23, 25, 26, 28, and 31 depend on claim 7. Applicants have amended claim 15 to recite a composition comprising a recombinant vaccine and a separate nucleic acid sequence. Claims 24, 29, and 32 depend on claim 15. The amendments to claims 7 and 15 obviate the basis of the rejection as it applies to claim 7, 8, 10, 15, 17, 23, 24, 28, 29, 31, and 32. Applicants respectfully request that the rejection of claims 7, 8, 10, 15, 17, 23, 24, 28, 29, 31, and 32 is withdrawn.

Claim Rejections under 35 USC § 103

Claims 1, 2, 4-8, 10-15, 17-19, 22-32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Boursnell in view of Rosen et al. (US Patent Application 2002/0044941A1). Applicants respectfully disagree fro two reasons: (1) the Office has improperly based its obviousness analysis on inherency; and (2) the Office has cited a reference that teaches away from the claimed invention.

As to the (1) above, the concepts of obviousness and inherency are distinct, and an obviousness rejection based upon inherency analysis is improper. *See, e.g., W.L. Gore &*

Associates, Inc. v. Garlock, Inc. , 721 F.2d 1540, 220 USPQ 303, 314 (Fed. Cir. 1983), cert. denied , 469 U.S. 851 (1984). The Office has improperly based its obviousness analysis on inherency. The rejection of claims 1, 2, 4-8, 10-15, 17-19, 22-32 under the 35 U.S.C. 103(a) as being unpatentable over Boursnell in view of Rosen is improper. Applicants respectfully request that the pending rejection be withdrawn.

As to (2) above, claim 1 recites a composition comprising: an isolated nucleic acid molecule that encodes an immunogen, wherein said immunogen is a pathogen antigen, a cancer-associated antigen or an antigen linked to cells associated with autoimmune diseases; and an isolated nucleic acid molecule that encodes one or more immunomodulating proteins selected from the group consisting of: Fos, c-jun, Sp-1, Ap-1, Ap-2, p38, p65Rel, MyD88, IRAK, TRAF6, IkB, Inactive NIK, SAP K, SAP-1, JNK, interferon response genes, NFkB, Bax, TRAIL, TRAILrec, TRAILrecDRC5, TRAIL-R3, TRAIL-R4, RANK, RANK LIGAND, Ox40, NKG2D, MICA, MICB, NKG2A, NKG2B, NKG2C, NKG2E, NKG2F, TAP1, TAP2; wherein the isolated nucleic acid sequence that encodes the immunogen occurs on a separate nucleic acid molecule from the nucleic acid sequence that encode one or more immunomodulating proteins. Claims 2, 4-6, 13, 22, 27, and 30 are dependent on claim 1.

Claim 7 recites a composition comprising: an isolated plasmid comprising a nucleotide sequence that encodes an immunogen operably linked to regulatory elements, wherein said immunogen is a pathogen antigen, a cancer-associated antigen or an antigen linked to cells associated with autoimmune diseases; in combination with a separate nucleotide sequence that encodes one or more immunomodulating proteins operably linked to regulatory elements, wherein said immunomodulating proteins are selected from the group consisting of: Fos, c-jun, Sp-I, Ap-1, Ap-2, p38, p65Rel, MyD88, IRAK, TRAF6, IkB, Inactive NIK, SAP K, SAP-1, INK, interferon response genes, NFkB, Bax, TRAIL, TRAILrec, TRAILrecDRC5, TRAIL-R3, TRAIL-R4, RANK, RANK LIGAND, Ox40, NKG2D, MICA, MICB, NKG2A, NKG2B, NKG2C, NKG2E, NKG2F, TAP1, TAP2. Claims 8, 10-12, 23, 25, 26, 28, and 31 depend on claim 7.

Claim 14 recites a method of inducing an immune response in an individual against an immunogen comprising administering to said individual a composition of claim 1.

Claim 15 recites a recombinant vaccine comprising a nucleotide sequence that encodes an immunogen operably linked to regulatory elements, wherein said immunogen is a pathogen antigen, a cancer-associated antigen or an antigen linked to cells associated with autoimmune diseases; in combination with a separate nucleotide sequence that encodes one or more immunomodulating proteins operably linked to regulatory elements, wherein said immunomodulating proteins are selected from the group consisting of: Fos, c-jun, Sp-1, Ap-1, Ap-2, p38, p65Rel, MyD88, IRAK, TRAF6, IkB, Inactive NIK, SAP K, SAP-1, JNK, interferon response genes, NFkB, Bax, TRAIL, TRAILrec, TRAILrecDRC5, TRAIL-R3, TRAIL-R4, RANK, RANK LIGAND, Ox40, NKG2D, MICA, MICB, NKG2A, NKG2B, NKG2C, NKG2E, NKG2F, TAP1, TAP2.

Boursnell discloses the use of non-replicative HSV viruses for transduction of cancer cells. Boursnell does not disclose, teach, or suggest a first and second nucleic acid sequences that encode an immunogen and OX40, respectively. Boursnell does not disclose, teach or suggest two separate nucleic acid molecules carrying the immunogen and the immunomodulating proteins of the instant invention. Boursnell does not disclose, teach, or suggest the stimulation of an antigen-specific immune response against an immunogen encoded by a nucleic acid sequence.

In stark contrast to the claimed invention, Boursnell discloses the modification of cancer cells for very specific use of the cancer cells themselves as an immunogen. For instance, Boursnell provides:

> Transduction takes place by infection of the live target cell by the viral vector in per-se known manner.
>
> Such a process can for example comprise treating a human or non-human animal cell to introduce heterologous genetic material into said cell to render said cell more highly immunogenic, comprising the steps of (a) providing a recombinant herpesviral vector which is an attenuated or replication-defective and non-transforming mutant herpesvirus, and which carries e.g. a gene encoding a heterologous immunomodulatory protein selected from

> cytokines and immunological co-stimulatory molecules and chemo-attractants, and (b) transducing malignant or nonmalignant human or non-human animal cells, which can be selected for example from: malignant cells related to blood cells, hemopoietic cells, malignant or non-malignant CD34+ cells, by contacting said cells with said virus vector to transduce said cells ***and render said cells more highly immunogenic.***

(Boursnell, column 4). The purpose of Boursnell is to deliver genetic material directly to a cancer cell of a host and have the cancer cell itself act as an immunogen. This is contrary to the claimed invention.

The claimed invention relates to the stimulation of an immune response based upon the administration of an antigen being encoded by cells that stimulate the immune response in combination with an adjuvant (immunomodulating protein). The immunogen of the claims stimulates the immune response, not a transduced cell.

In combining the references, the Office has picked out those passages which support their position with respect to a *prima facie* case of obviousness and disregarded those teachings which teach away and do not support the prima facie case of obviousness. This is improper and expressly contrary to a well established legal precedent. The references must be viewed in their entirety and portions which teach away from the invention must be considered. When all of the teachings of the references are taken into account, it is overwhelmingly clear that the combination of references is improper and therefore does not produce a prima facie case of obviousness. Boursnell specifically teaches away from the claimed invention.

Rosen discloses a lung cancer treatment in which OX40 protein is administered to a patient. One of ordinary skill in the art would not recognize a benefit to providing nucleic acid constructs that encode OX40 in place of the recombinant protein administered in Rosen. One of ordinary skill in the art would not identify a recognizable benefit to ensuring two separate nucleic acid molecules expressing an immunogen or immunomodulating protein of the claimed invention. Therefore, the combination of references does not teach each and every element of the claims.

Claims 18 and 19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Boursnell in view of Hodge et. al. (JNCI 2000, Vol. 92, No. 15, pages 1228-1239). Applicants respectfully traverse.

Boursnell is discussed above and teaches away the claimed invention.

Hodge discloses the administration of a fowlpox vector expressing LFA-3, B7-1, and ICAM-1. Hodge does not disclose, teach, or suggest OX40. Hodge does not disclose, teach or suggest two separate nucleic acid molecules expressing an immunogen or immunomodulating protein of the claimed invention. One of ordinary skill in the art would not recognize a benefit to providing nucleic acid constructs that encode OX40 in place of the three administered in Hodge. One of ordinary skill in the art would not identify a recognizable benefit to ensuring two separate nucleic acid molecules expressing an immunogen or immunomodulating protein of the claimed invention. Therefore, the combination of references does not teach each and every element of the claims.

The combination of Brousnell and Hodge does not render the invention recited in claims 18 and 19 obvious because the combination of each reference fails to teach the elements of the claims. As discussed above, Boursnell teaches away from the claimed invention.

Applicants respectfully request that the rejection of claims 1, 2, 4-8, 10-15, 17-19, 22-32 under 35 U.S.C. 103 (a) as being unpatentable over Boursnell et al. (US2003/0113919A1) in view of Rosen or Hodge be withdrawn.

Claim Rejections under 35 USC § 112, Second Paragraph

Claims 22-24, 28, and 29 stand rejected under stand rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claims the subject matter which Applicants regards as the invention. The Office asserts that

Claims 22-24, 28, and 29 are indefinite because the metes and bounds of the term "protein encodes OX40" cannot be determined from the language of the claims.

Applicants respectfully disagree and traverse the rejection, but solely in the interest of expediting prosecution have amended the claims to recite " wherein the nucleotide sequence that encodes one or more immunomodulating proteins" encodes OX40. The amendment renders the language of the claim more precise. It is clear that nucleotide sequence that encodes one or more immunomodulating proteins is the sequence that encodes OX40. The amendments obviate the basis of the rejection.

One of ordinary skill in the art would easily comprehend what the metes and bounds of the terms mean in light of the plain language of the claims and the relevant disclosure in the specification. Claims 22-24, 28, and 29 are definite within the meaning of 35 U.S.C. §112. Accordingly, Applicants respectfully request that the rejection of claims 22-24, 28, and 29 under 35 U.S.C. §112, second paragraph be withdrawn.

Claim Rejections under 35 USC § 112, First Paragraph

Claims 1-2, 4-8, 10-15, 17-19, and 22-26 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly failing the written description requirement. Applicants respectfully disagree but solely in the interest of expediting prosecution have amended the claims to remove recitation of "fragments thereof." The amendment obviates the basis of the rejection. Applicants respectfully request that the rejection of Claims 1-2, 4-8, 10-15, 17-19, and 22-26 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 15, 17, 18, 19, 24, 29, and 32 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly failing the enablement requirement. More specifically, the Office asserts that one of ordinary skill in the art would require undue experimentation to use and or make the claimed invention. Applicants respectfully disagree.

Applicants note that it is well established that the Office has the initial burden of establishing that a claimed invention does not meet the enablement requirement. The description

of the invention is presumed to be enabled and, in order to sustain an enablement rejection under the first paragraph of 35 U.S.C. § 112, the Examiner must establish doubt in the objective truth of Applicant's assertion that the claimed invention is enabled using reasoning and evidence of those skilled in the art. See, e.g. *In re Marzocchi* , 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). See also M.P.E.P. § 2163.

Applicants respectfully urge that the evidence and reasoning in the specification supports the conclusion that one skilled in the art would accept Applicant's assertion that the claims are enabled by the specification. The Office has cited one reference that discloses a proffered mechanism of OX40 activity. Nothing in the reference discloses or suggests that the claimed invention would not work. On the contrary, there is no disclosure in the reference that describes administering nucleic acid sequences that encodes an immunogen, much less the a nucleic acid sequence that encodes an immunogen in combination with a nucleic acid sequence that encodes OX40. There is no legal basis for any deficiency in knowing exact mechanism of a particular method for a particular composition. The Redmond reference is therefore woefully insufficient to support an enablement rejection on its own.

The Lederman reference is erroneously designated as illustrative of the state-of-the-art. The Lederman reference was published in 1991, no fewer than 12 years from the priority date of the instance application. To say that one of ordinary skill in the art in 1991 was equivalent to the same person of ordinary skill in 2003 is wholly without merit.

The Office has failed to set forth any credible or sufficient reasoning or evidence to support the rejection. The Office has not established that the claimed invention does not meet the enablement requirement. Failing to do so, the burden to demonstrate enablement is not properly shifted to Applicants.

Not withstanding the failure of the Office to meet its burden of proof, Applicants provide the following evidence of the claims being fully supported by the disclosures in the specification. The examples of the specification provide a list of each immunomodulating protein of the claimed invention. The examples of the specification provide a list of no fewer than 25 different families of pathogens from which antigens can be derived. The examples clearly demonstrate,

design, expression, and in vivo data demonstrating the effect of some of these variants on the immune system of mice. The examples also clearly demonstrate that one particular immunomodulating protein was able to stimulate an immune response against HIV-1 in mice. The claims are enabled by these disclosures. One of ordinary skill in the art would be able to practice the invention without undue experimentation. Pages 32-33 disclose no fewer than 21 different issued patents around. In support of the enablement of recombinant vaccines such as the ones contemplated by the invention, Applicants have attached the abstract of Earl et al., which clearly discloses that design, construction, and isolation of recombinant vaccinia viruses was well within the ability of one of ordinary skill of the art at the time the application was filed.

Applicants respectfully request that the rejection of claims 15, 17, 18, 19, 24, 29, and 32 under 35 U.S.C. §112, first paragraph, be withdrawn.

Conclusion

Claims 1, 2, 4-7, 10-15, 17-19 and 22-32 are in condition for allowance. A notice of allowance is earnestly solicited. Applicants invite the Examiner to contact the undersigned at 610.640.7852 to clarify any unresolved issues raised by this response.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully submitted,

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Enclosed: Earl et. al., *Current Protocols in Protein Science*, 2001; May